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Role of inositol 1,4,5-trisphosphate receptors in regulating apoptotic signaling and heart failure.

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The inositol 1,4,5-trisphosphate receptor (IP3R) is an endoplasmic reticular calcium release channel found in most cell types. Calcium signaling mediated by IP3Rs regulates a wide variety of physiological processes, including smooth muscle contraction, immune function, and fertility. We have focused on the role of the IP3R in programmed cell death and the regulation of IP3R levels in heart failure, a condition shown to be associated with cardiomyocyte apoptosis. During end-stage human heart failure, we have demonstrated that type 1 IP3R (IP3R1) mRNA and protein levels are up-regulated, in contrast to other cardiac calcium regulatory proteins, such as the type 2 ryanodine receptor (RYR2) and type IIa sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2), which are down-regulated. These data suggest that altered calcium channel expression may contribute to the defects in calcium homeostasis during heart failure. Furthermore, regulation of the IP3R may have implications for the survival of cardiac myocytes. Data from our laboratory have linked IP3R expression with susceptibility to apoptosis. IP3R-deficient T cells are resistant to apoptosis induced by dexamethasone, T cell receptor stimulation, ionizing radiation, and Fas. These findings suggest that intracellular calcium release via IP3Rs is a critical mediator of apoptosis. Thus the IP3R, which is up-regulated during human heart failure, may play a role in cardiomyocyte apoptosis and therefore in the pathophysiology of heart failure.